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(54) FORME POSOLOGIQUE ANTI-ABUS POUR ADMINISTRATION PAR VOIE ORALE CONTENANT DU (1R, 2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYL-PROPYL)-PHENOL

(54) ORAL DOSAGE FORM SAFEGUARDED AGAINST ABUSE CONTAINING (1R, 2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYL-PROPYL)-PHENOL

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(54) Titre : FORME POSOLOGIQUE ANTI-ABUS POUR ADMINISTRATION PAR VOIE ORALE CONTENANT DU (1R, 2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYL-PROPYL)-PHENOL

(54) Title: ORAL DOSAGE FORM SAFEGUARDED AGAINST ABUSE CONTAINING (1R, 2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYL-PROPYL)-PHENOL

(57) Abrégé/Abstract:
The invention relates to an oral dosage form, which is safeguarded against abuse and which has a controlled release of (1R, 2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol for a once daily administering. The invention is characterized in that the oral dosage form comprises the active ingredient and/or one or more pharmaceutically acceptable compounds (A) thereof, at least one synthetic and/or natural polymer (C), retarding adjuvants, optionally comprises additional physiologically compatible adjuvants (B), and optionally comprises a wax (D). The oral dosage form has a breaking resistance of at least 500 N, preferably at least 750 N. The dosage form contains at least one of the following abuse-preventing constituents (a)-(f); (a) at least one substance that irritates the nasal and/or pharyngeal cavity; (b) at least one viscosity-increasing agent; (c) at least one antagonist for the active ingredient having an abuse potential; (d) at least one emetic; (e) at least one colorant serving as an aversive agent, and; (f) at least one bitter substance.

Abstract

The present invention relates to an abuse-proofed, oral dosage form with controlled release of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol for once daily administration, characterised in that it comprises the active ingredient and/or one or more of the pharmaceutically acceptable compounds thereof (A), at least one synthetic and/or natural polymer (C), delayed-release auxiliary substances, optionally further physiologically acceptable auxiliary substances (B) and optionally a wax (D), wherein the dosage form in each case exhibits a breaking strength of at least 500 N, preferably of at least 750 N. The dosage form contains at least one of the following abuse-preventing components (a)-(f): (a) at least one substance which irritates the nasal passages and/or pharynx, (b) at least one viscosity-increasing agent, (c) at least one antagonist for the active ingredient with potential for abuse, (d) at least one emetic, (e) at least one dye as an aversive agent, (f) at least one bitter substance.

Oral dosage form safeguarded against abuse containing (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol

The present invention relates to an abuse-proofed, oral dosage form with controlled release of the active ingredient (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol for once daily administration, which dosage form comprises the active ingredient and/or one or more of the pharmaceutically acceptable salts and/or derivatives thereof (A), at least one synthetic or natural polymer (C), optionally delayed-release matrix materials, optionally physiologically acceptable auxiliary substances (B) and optionally a wax (D), component (C) or (D) in each case exhibiting a breaking strength of at least 500 N.

This active ingredient also exhibits, apart from an excellent pain-relieving action, abuse potential, i.e. it may be used by an abuser to bring about an action which does not correspond to its intended purpose. This active ingredient is accordingly used by abusers, for example, to induce a state of narcosis or euphoria.

These dosage forms containing active ingredient are frequently used for long-term treatment, for example for chronic pain or pain caused by tumours. In long-term treatment, in particular, it is important to enable the patient to enjoy a good quality of life. The measures which improve the quality of life of a patient include dosage forms which allow once daily administration. However, because of the relatively large quantity of active ingredient, such dosage forms, which provide delayed release of the active ingredient, are particularly attractive to the abuser in order to induce the desired state of narcosis or euphoria as quickly as possible.

Since, however, delayed-release dosage forms containing the stated active ingredient do not usually give rise to the kick desired by the abuser when taken orally even in abusively high quantities, these dosage forms for example in the form of tablets or capsules are also comminuted, e.g. ground, and sniffed by the abuser for the purpose of abuse or the active ingredients are preferably extracted from the powder obtained in this way by means of an aqueous liquid and the resultant solution is administered parenterally, in particular intravenously, optionally after filtration

through cotton wool or cellulose wadding. This type of administration produces further accelerated increase in active ingredient level than with oral or nasal abuse, with the result desired by the abuser, namely the kick.

US-A-4,070,494 proposed adding a swellable agent to the dosage form in order to prevent abuse. When water is added to extract the active ingredient used therein, this agent swells and ensures that the filtrate separated from the gel contains only a small quantity of active ingredient.

The multilayer tablet disclosed in WO 95/20947 is based on a similar approach to preventing parenteral abuse, said tablet containing an active ingredient with potential for abuse and at least one gel former, each in different layers.

WO 03/015531 A2 discloses another approach to preventing parenteral abuse. A dosage form containing an analgesic opioid and a dye as an aversive agent is described therein. The colour released by tampering with the dosage form is intended to discourage the abuser from using the dosage form which has been tampered with.

Another known option for complicating abuse involves adding to the dosage form an antagonist to the active ingredient, such as for example naloxone or naltrexone, or compounds which cause a physiological defence response, such as for example ipecacuanha (ipecac) root, or bitter substances.

Since, however, as in the past, it is in most cases necessary for the purposes of abuse to pulverise dosage forms with controlled release of the active ingredient, it was the object of the present invention to complicate or prevent the pulverisation which precedes abuse of dosage forms with controlled release of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol with the means conventionally available to the potential abuser and in this manner to provide a dosage form for the active ingredient, which, when correctly administered, ensures the desired therapeutic action with once daily administration, but from which the active ingredient cannot be converted into a form suitable for abuse simply by pulverisation.

This object has been achieved by the provision of the abuse-proofed, oral dosage form according to the invention with controlled release of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol for once daily administration, which dosage form, apart from the active ingredient and/or one or more of the pharmaceutically acceptable compounds thereof, preferably salts or derivatives, preferably esters, ethers or amides and the corresponding stereoisomers and/or the corresponding pharmaceutically acceptable compounds or derivatives thereof (A), comprises at least one synthetic and/or natural polymer (C), at least one delayed-release auxiliary substance (E), optionally at least one further physiologically acceptable auxiliary substance (B) and optionally a wax (D), component (C) or (D) in each case exhibiting a breaking strength of at least 500 N, preferably of at least 750 N.

By using components (C) and optionally (D) with the stated minimum breaking strength (measured as disclosed in the present application), preferably in such quantities that the dosage form also exhibits such a minimum breaking strength of at least 500 N, preferably at least 750 N, pulverisation of the dosage form with conventional means and thus subsequent abuse, preferably nasal or parenteral abuse, may be considerably complicated or prevented.

Without sufficient comminution of the dosage form, non-hazardous parenteral, in particular intravenous or nasal administration is impossible or extraction of the active ingredient from this dosage form takes the abuser too long, or no or an inadequate kick is obtained on abusive oral administration, since spontaneous release does not occur.

According to the invention, comminution is taken to mean pulverisation of the dosage form with conventional means which are conventionally available to an abuser, such as for example a pestle and mortar, a hammer, a mallet or other usual means for pulverisation by application of force.

The dosage form according to the invention is thus suitable for preventing the parenteral, nasal and/or oral abuse of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-

propyl)phenol. The active ingredient is known from EP-A-0 693 475 as an analgesically active pharmaceutical preparation.

The active ingredient (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol may not only be used as such, i.e. as the free base, but also in the form of one of the pharmaceutically acceptable salts thereof, solvates, a pharmaceutically acceptable derivative, in particular as an amide, ester or ether, and/or the corresponding stereoisomers and/or the corresponding pharmaceutically acceptable compounds thereof. Production of the active ingredient is also known from EP-A-0 693 475 A1.

In the dosage form according to the invention, the content of active ingredient is preferably between 0.5 and 80 wt.%, particularly preferably between 10 and 40 wt.% and very particularly preferably between 5-50 wt.%.

The dosage form according to the invention contains (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol as such and/or as a pharmaceutically acceptable compound conventionally in a quantity of 2.5 to 1,000 mg, in particular of 5 to 800 mg, very particularly preferably of 5-600 mg calculated as (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol per dosage form or dosage unit.

According to the invention, pharmaceutically acceptable salts of the active ingredient are salts which, when used pharmaceutically, in particular when correctly administered to mammals or humans, in particular humans, are physiologically acceptable. Such pharmaceutical salts may, for example, be salts with inorganic or organic acids, such as for example preferably the hydrochloride, hydrobromide, saccharinate, sulphate, the salt with methanesulphonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid and/or aspartic acid, very particularly preferably, the hydrochloride is used as the salt.

In order to achieve the necessary breaking strength of the dosage form according to the invention, at least one synthetic, semi-synthetic and/or natural polymer (C) is used which has a breaking strength, measured using the method disclosed in the present application, of at least 500 N, preferably of 750 N. Preferably, at least one

polymer is selected for this purpose from among the group comprising polyalkylene oxides, preferably polymethylene oxides, polyethylene oxides, polypropylene oxides, polyolefins, preferably polyethylenes, polypropylenes, polyvinyl chlorides, polycarbonates, polystyrenes, poly(meth)acrylates, the copolymers thereof, and mixtures of at least two of the stated polymer classes or polymers. Particularly preferably, a water-soluble or water-swellable polymer is used. Thermoplastic polyalkylene oxides of high molecular weight are preferred. Polyethylene oxides with a molecular weight of at least 0.5 million, preferably of at least 1 million, particularly preferably of 1 million to 15 million, determined by rheological measurement, are particularly preferred. These polyethylene oxides have a viscosity at 25°C of 4500 to 17600 cP, measured on a 5 wt.% aqueous solution of the polymer using a model RVF Brookfield viscosimeter (spindle no. 2 / rotational speed 2 rpm), of 400 to 4000 cP, measured on a 2 wt.% aqueous solution of the polymer using the stated viscosimeter (but with spindle no. 1 or 3 / rotational speed 10 rpm) or of 1650 to 10000 cP, measured on a 1 wt.% aqueous solution of the polymer using the stated viscosimeter (but with spindle no. 2 / rotational speed 2 rpm) (cf. Handbook of Pharmaceutical Excipients by Raymond C. Rowe, among others, 4th edition, 2003, page 460).

The polymers are preferably used as powder to produce the dosage form according to the invention. They can be water-soluble or water-swellable.

Preferably, the component (C) is used in a quantity of 20 to 99.9 wt.%, particularly preferably of at least 35 wt.%, very particularly preferably of at least 50 wt.%, relative to the total weight of the dosage form.

As auxiliary substances (B), the auxiliary substances conventionally known for the formulation of solid dosage forms can be used. Preferably, these are plasticisers such as polyethylene glycol, auxiliary substances which affect the release of active ingredient, as listed below, preferably hydrophobic or hydrophilic, preferably hydrophilic polymes, very particularly preferably hydroxypropylmethylcellulose or hydroxpropylcellulose, and/or antioxidants. Ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, salts of ascorbic acid, monothioglycerol, phosphorous acid, vitamin C, vitamin E and the derivatives thereof, sodium bisulphite, particularly

preferably butylated hydroxytoluene (BHT) or butylated hydroxyanisole (BHA) and α-tocopherol are suitable as antioxidants.

The antioxidant is preferably used in quantities of 0.01 to 10 wt.%, preferably 0.03 to 5 wt.%, relative to the total weight of the dosage form.

Moreover, in addition to the above-stated polymers, at least one natural, semi-synthetic or synthetic wax (D) with a breaking strength, measured using the method disclosed in the present application, of at least 500 N, preferably of 750 N, may additionally be used to achieve the necessary breaking strength of the dosage form according to the invention. Waxes with a softening point of at least 60°C are preferred. Carnauba wax and beeswax are particularly preferred. Carnauba wax is very particularly preferred. Carnauba wax is a natural wax which is obtained from the leaves of the carnauba palm and has a softening point of at most 90°C. When additionally using the wax component, the latter is used together with at least one polymer (C), preferably a polyethylene oxide, in such quantities that the dosage form exhibits a breaking strength of at least 500 N, preferably of at least 750 N, measured using the method stated in the present application.

The dosage forms according to the invention are distinguished in that they cannot be pulverised using conventional comminution tools, such as pestle and mortar, due to their hardness. Oral, parenteral, in particular intravenous, or nasal abuse is thereby virtually ruled out altogether. However, in order to prevent any possible abuse of the dosage forms according to the invention, in a preferred embodiment, the dosage forms according to the invention may contain further abuse-complicating or -preventing agents as auxiliary substances (B).

Thus, the abuse-proofed dosage form according to the invention may comprise, in addition to the active ingredient used according to the invention, at least one polymer (C) and optionally at least one wax (D), at least one of the following components (a)-(e) as auxiliary substances (B):

(a) at least one substance which irritates the nasal passages and/or pharynx,

(b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, preferably as an aqueous extract obtained from the dosage form, forms a gel which preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

(c) at least one antagonist for the active ingredient used,

(d) at least one emetic,

(e) at least one dye as an aversive agent,

(f) at least one bitter substance.

The components (a) to (f) are each additionally suitable on their own as additional protection of the dosage form according to the invention against abuse. Accordingly, component (a) is preferably suitable for proofing the dosage form against nasal, oral and/or parenteral, preferably intravenous, abuse, component (b) is preferably suitable for proofing against parenteral, particularly preferably intravenous and/or nasal abuse, component (c) is preferably suitable for proofing against nasal and/or parenteral, particularly preferably intravenous, abuse, component (d) is preferably suitable for proofing against parenteral, particularly preferably intravenous, and/or oral and/or nasal abuse, component (e) is suitable as a visual deterrent against oral or parenteral abuse and component (f) is suitable for proofing against oral or nasal abuse. Through the co-use of at least one of the above-stated components, it is possible to complicate abuse even more effectively for the dosage forms according to the invention.

In one embodiment, the dosage form according to the invention may also comprise two or more of components (a)-(f) in a combination, preferably in the combinations (a), (b) and optionally (c) and/or (f) and/or (e) or (a), (b) and optionally (d) and/or (f) and/or (e).

In another embodiment, the dosage form according to the invention may comprise all of components (a)-(f).

If the dosage form according to the invention comprises component (a) as additional protection against abuse, substances which irritate the nasal passages and/or pharynx which may be considered according to the invention are any substances which, when administered via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the abuser that he/she does not wish to or cannot continue administration, for example burning, or physiologically counteract taking of the active ingredient, for example due to increased nasal secretion or sneezing. These substances which conventionally irritate the nasal passages and/or pharynx may also bring about a very unpleasant sensation or even unbearable pain when administered parenterally, in particular intravenously, such that the abuser does not wish to or cannot continue administration.

Particularly suitable substances which irritate the nasal passages and/or pharynx are those which cause burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli. Appropriate substances and the quantities thereof which are conventionally to be used are known per se to the person skilled in the art or may be identified by simple preliminary testing.

The substance which irritates the nasal passages and/or pharynx of component (a) is preferably based on one or more constituents or one or more plant parts of at least one hot substance drug.

Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pages 82 et seq. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

A dosage unit is taken to mean a separate or separable administration unit, such as for example a tablet or a capsule.

One or more constituents of at least one hot substance drug selected from the group consisting of Allii sativi bulbus (garlic), Asari rhizoma cum herba (Asarum root and leaves), Calami rhizoma (calamus root), Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper), Curcumae longae rhizoma (turmeric root), Curcumae xanthorrhizae rhizoma (Javanese turmeric root), Galangae rhizoma (galangal root), Myristicae semen (nutmeg), Piperis nigri fructus (pepper), Sinapis albae semen (white mustard seed), Sinapis nigri semen (black mustard seed), Zedoariae rhizoma (zedoary root) and Zingiberis rhizoma (ginger root), particularly preferably from the group consisting of Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper) and Piperis nigri fructus (pepper) may preferably be added as component (a) to the dosage form according to the invention.

The constituents of the hot substance drugs preferably comprise o-methoxy(methyl)phenol compounds, acid amide compounds, mustard oils or sulphide compounds or compounds derived therefrom.

Particularly preferably, at least one constituent of the hot substance drugs is selected from the group consisting of myristicin, elemicin, isoeugenol, α-asarone, safrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, capsaicin derivatives, such as N-vanillyl-9E-octadecenamide, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, norcapsaicin and nomorcapsaicin, piperine, preferably trans-piperine, glucosinolates, preferably based on non-volatile mustard oils, particularly preferably based on p-hydroxybenzyl mustard oil, methylmercapto mustard oil or methylsulphonyl mustard oil, and compounds derived from these constituents.

The dosage form according to the invention may preferably also contain plant parts of the corresponding hot substance drugs in a quantity of 0.01 to 30 wt.%, particularly preferably of 0.1 to 0.5 wt.%, in each case relative to the total weight of the dosage unit.

If one or more constituents of corresponding hot substance drugs are used, the quantity thereof in a dosage unit according to the invention preferably amounts to 0.001 to 0.005 wt.%, relative to the total weight of the dosage unit.

Another option for additionally preventing abuse of the dosage form according to the invention consists in adding at least one viscosity-increasing agent as a further abuse-preventing component (b) to the dosage form, which, with the assistance of a necessary minimum quantity of an aqueous liquid, preferably as an aqueous extract obtained from the dosage form, forms a gel which is virtually impossible to administer safely and preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid.

For the purposes of the present application visually distinguishable means that the active ingredient-containing gel formed with the assistance of a necessary minimum quantity of aqueous liquid, when introduced, preferably with the assistance of a hypodermic needle, into a further quantity of aqueous liquid at 37°C, remains substantially insoluble and cohesive and cannot straightforwardly be dispersed in such a manner that it can safely be administered parenterally, in particular intravenously. The material preferably remains visually distinguishable for at least one minute, preferably for at least 10 minutes.

Increasing the viscosity to a gel makes it more difficult or even impossible for it to be passed through a needle or injected. If the gel remains visually distinguishable, this means that the gel obtained on introduction into a further quantity of aqueous liquid, for example by injection into blood, initially remains in the form of a largely cohesive thread, which, while it may indeed be broken up mechanically into smaller fragments, cannot be dispersed or even dissolved in such a manner that it can safely be administered parenterally, in particular intravenously. In combination with at least one further present component (a), (d) to (f), this additionally leads to unpleasant burning, vomiting, bad flavour and/or visual deterrence.

Intravenous administration of such a gel would most probably result in obstruction of blood vessels, associated with serious damage to the health of the abuser.

In order to verify whether a viscosity-increasing agent is suitable as component (b) for use in the dosage form according to the invention, the active ingredient is mixed with the viscosity-increasing agent and suspended in 10 ml of water at a temperature of 25°C. If this results in the formation of a gel which fulfils the above-stated

conditions, the corresponding viscosity-increasing agent is suitable for additionally preventing or averting abuse of the dosage forms according to the invention.

If component (b) is added to the dosage form obtained by the process according to the invention, preferably one or more viscosity-increasing agents are used, which are selected from the group comprising microcrystalline cellulose with 11 wt.% carboxymethylcellulose sodium (Avicel® RC 591), carboxymethylcellulose sodium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), locust bean flour (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), pectins, preferably from citrus fruits or apples (Cesapectin® HM Medium Rapid Set), waxy maize starch (C*Gel 04201®), sodium alginate (Frimulsion ALG (E401)®) guar flour (Frimulsion BM®, Polygum 26/1-75®), iota-carrageenan (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat 150 ®), tara stone flour (Polygum 43/1®), propylene glycol alginate (Protanal-Ester SD-LB®), sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide welan gum (K1A96), xanthans such as xanthan gum (Xantural 180®). Xanthans are particularly preferred. The names stated in brackets are the trade names by which the materials are known commercially. In general, preferably a quantity of 0.1 to 20 wt.%, particularly preferably 0.1 to 15 wt.%, relative to the total quantity of the dosage form, of the stated viscosity-increasing agent(s) is sufficient to fulfil the above-stated conditions.

The component (b) viscosity-increasing agents, where provided, are preferably present in the dosage form according to the invention in quantities of at least 5 mg per dosage unit, i.e. per administration unit.

In a particularly preferred embodiment of the present invention, the viscosity-increasing agents used as component (b) are those which, preferably by extraction from the dosage form with the necessary minimum quantity of aqueous liquid, form a gel which encloses air bubbles. The resultant gels are distinguished by a turbid appearance, which provides the potential abuser with an additional optical warning and discourages him/her from administering the gel parenterally.

Component (C) may also optionally serve as an additional viscosity-increasing agent, which forms a gel with the assistance of a necessary minimum quantity of aqueous liquid.

It is also possible, to arrange the viscosity-increasing component and the other constituents of the dosage form according to the invention spatially separately from one another.

Moreover, in order to discourage and prevent abuse, the dosage form according to the invention may furthermore comprise component (c), namely one or more antagonists for the active ingredient used, wherein the antagonist is preferably spatially separated from the remaining constituents of the dosage form according to the invention and, when correctly used, should not exert any effect.

Suitable antagonists for preventing the abuse of the active ingredient used are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

The antagonist used is preferably a substance selected from the group comprising naloxone, naltrexone, nalmefene, nalide and nalmexone, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate. The corresponding antagonist components, where component (c) is provided, are preferably used in a quantity of at least 1 mg, particularly preferably in a quantity of 3 to 100 mg, very particularly preferably in a quantity of 5 to 50 mg per dosage form, i.e. per administration unit.

The dosage form according to the invention preferably comprises the antagonist component in a conventional therapeutic dose known to the person skilled in the art, particularly preferably in a quantity of twice to three times this dose per administration unit in comparison to the conventional dose.

If the combination for additional discouragement and prevention of abuse of the dosage form according to the invention comprises component (d), it may comprise at least one emetic, which is preferably present in a spatially separated arrangement from the other components of the dosage form according to the invention and, when correctly used, is intended not to exert its effect in the body.

Suitable emetics for additionally preventing abuse of the dosage form according to the invention are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

An emetic based on one or more constituents of ipecacuanha (ipecac) root, preferably based on the constituent emetine, may preferably be considered for the dosage form according to the invention, as are, for example, described in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd revised edition, Gustav Fischer Verlag, Stuttgart, New York 1982. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

The dosage form according to the invention may preferably comprise the emetic emetine as component (d), preferably in a quantity of at least 3 mg, particularly preferably of at least 10 mg and very particularly preferably in a quantity of at least 20 mg per dosage form, i.e. administration unit.

Apomorphine may likewise preferably be used as an emetic for additional abuse-proofing, preferably in a quantity of preferably at least 3 mg, particularly preferably of at least 5 mg and very particularly preferably of at least 7 mg per administration unit.

If the dosage form according to the invention contains component (e) as an additional abuse-preventing auxiliary substance, the use of such a dye brings about an intense coloration of a corresponding aqueous solution, in particular when the attempt is made to extract the active ingredient for parenteral, preferably intravenous

administration, which coloration may act as a deterrent to the potential abuser. Oral abuse, which conventionally begins by means of aqueous extraction of the active ingredient, may also be prevented by this coloration. Suitable dyes and the quantities required for the necessary deterrence may be found in WO 03/015531, wherein the corresponding disclosure should be deemed to be part of the present disclosure and is hereby introduced as a reference.

If the dosage form according to the invention contains component (f) as a further abuse-preventing auxiliary substance, this addition of at least one bitter substance and the consequent impairment of the flavour of the dosage form additionally prevent oral and/or nasal abuse.

Suitable bitter substances and the quantities effective for use may be found in US-2003/0064099, the corresponding disclosure of which should be deemed to be the disclosure of the present application and is hereby introduced as a reference. Suitable bitter substances are preferably aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, preferably aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate (Bitrex® ?); denatonium benzoate is particularly preferably used.

To ensure once daily administration, the dosage form according to the invention comprises the active ingredient at least in part in delayed-release form, wherein the delayed release of the active ingredient may be achieved with the assistance of conventional materials and processes known to the person skilled in the art, for example by embedding the active ingredient in a delayed-release matrix or by applying one or more delayed-release coatings. Active ingredient release must, however, be controlled such that the above-stated conditions are fulfilled in each case, for example that, in the event of correct administration of the dosage form, the active ingredient is virtually completely released before the optionally present component (c) and/or (d) can exert an impairing effect. In particular, release of the active ingredient must ensure analgesic action for at least 24 hours.

If release of the active ingredient from the dosage form according to the invention is controlled with the assistance of at least one delayed-release coating, the delayed-release coating may consist of conventional materials known to the person skilled in the art.

In a preferred embodiment of the dosage forms according to the invention, the delayed-release coating is preferably based on a water-insoluble, optionally modified natural and/or synthetic polymer or on a natural, semi-synthetic or synthetic wax or on a fat or a fatty alcohol or on a mixture of at least two of the above-stated components.

To produce a delayed-release coating, the water-insoluble polymers preferably comprise poly(meth)acrylates, particularly preferably poly(C_{1-4})-alkyl(meth)acrylates, poly(C_{1-4})-dialkylamino-(C_{1-4})-alkyl(meth)acrylates and/or the copolymers thereof, very particularly preferably copolymers of ethyl acrylate and methyl methacrylate with a molar ratio of monomers of 2:1 (Eudragit NE30D®), copolymers of ethyl acrylate, methyl methacrylate and trimethylammonium methyl methacrylate chloride with a molar ratio of monomers of 1:2:0.1 (Eudragit RS®), copolymers of ethyl acrylate, methyl methacrylate and trimethylammonium methyl methacrylate chloride with a molar ratio of monomers of 1:2:0.2 (Eudragit RL®) or a mixture of at least two of these above-stated copolymers. These coating materials are commercially obtainable as 30 wt.% aqueous latex dispersions, i.e. as Eudragit RS30D®, Eudragit NE30D® or Eudragit RL30D® and are preferably also used as such as coating material.

It is likewise preferable to use as water-insoluble polymers for the production of a delayed-release coating for the dosage forms according to the invention polyvinyl acetates optionally in combination with further auxiliary substances. These are commercially obtainable as aqueous dispersions containing 27 wt.% of polyvinyl acetate, 2.5 wt.% of povidone and 0.3 wt.% of sodium lauryl sulphate (Kollicoat SR 30 D®).

In a further preferred embodiment, the delayed-release coatings for the dosage form according to the invention are based on water-insoluble cellulose derivatives, preferably alkylcelluloses, such as for example ethylcellulose, or cellulose esters,

such as for example cellulose acetate. The coatings of ethylcellulose or cellulose acetate are preferably applied from an aqueous pseudolatex dispersion. Aqueous ethylcellulose pseudolatex dispersions are commercially obtainable as 30 wt.% dispersions (Aquacoat®) or as 25 wt.% dispersions (Surelease®).

If the delayed-release coating is based on a water-insoluble, optionally modified natural and/or synthetic polymer, the coating dispersion or solution may comprise, in addition to the corresponding polymer, a conventional physiologically acceptable plasticiser known to the person skilled in the art, in order to reduce the necessary minimum film temperature.

Suitable plasticisers are for example lipophilic diesters from an aliphatic or aromatic dicarboxylic acid with C_6-C_{40} and an aliphatic alcohol with C_1-C_8, such as for example dibutyl phthalate, diethyl phthalate, dibutyl sebacate or diethyl sebacate, hydrophilic or lipophilic esters of citric acid, such as for example triethyl citrate, tributyl citrate, acetyl tributyl citrate or acetyl triethyl citrate, polyethylene glycols, propylene glycol, esters of glycerol, such as for example triacetin, Myvacet® (acetylated mono- and diglycerides, $C_{23}H_{44}O_5$ to $C_{25}H_{47}O_7$), medium-chain triglycerides (Miglyol®), oleic acid or mixtures of at least two of the stated plasticisers. Aqueous dispersions of Eudragit RS® and optionally Eudragit RL® preferably contain triethyl citrate.

Preferably, a delayed-release coating for the dosage form according to the invention contains plasticisers in quantities of 5 to 50 wt.%, particularly preferably 10 to 40 wt.% and very particularly preferably 10 to 30 wt.%, relative to the quantity of polymer used. In individual cases, for example for cellulose acetate, it is also possible to use larger quantities of plasticisers.

Moreover, a delayed-release coating may comprise further conventional auxiliary substances known to the person skilled in the art, such as for example slip agents, preferably talcum or glycerol monostearate, colouring pigments, preferably iron oxides or titanium dioxide, or surfactants, such as for example Tween 80®.

The release profile of the active ingredient may furthermore be adjusted by conventional options known to the person skilled in the art, such as for example the

thickness of the coating or by the use of further auxiliary substances as constituents of the coating. Suitable auxiliary substances are for example hydrophilic or pH-dependent pore formers, such as for example sodium carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate, lactose, polyethylene glycol or mannitol or water-soluble polymers, such as for example polyvinylpyrrolidone or water-soluble celluloses, preferably hydroxypropylmethylcellulose or hydroxypropylcellulose.

The dosage forms according to the invention for release of the active ingredient used may additionally also comprise a coating which is resistant to gastric juices, which dissolves in pH-dependent manner. This coating makes it possible to ensure that the dosage forms according to the invention pass through the stomach undissolved and the active ingredient is not released until it reaches the intestine.

The coating resistant to gastric juices is preferably based on methacrylic acid/alkyl methacrylate copolymers, preferably methyl methacrylate, such as methacrylic acid or ethyl methacrylate copolymers with a molar ratio of the particular monomers of 1:1 to 1:2, such as Eudragit L®, Eudragit S®, Eudragit L30D-55®.

A delayed-release coating may be applied by conventional methods known to the person skilled in the art, such as for example by spraying of solutions, dispersions or suspensions, by melt methods or by powder application methods. The solutions, dispersions or suspensions may be used in the form of aqueous or organic solutions or dispersions. Aqueous dispersions are preferably used in this connection. Organic solvents which may be used are alcohols, for example ethanol or isopropanol, ketones, such as for example acetone, esters, for example ethyl acetate, wherein alcohols and ketones are preferably used. The coating methods are known from the prior art, for example H. Sucker, Georg Thieme Verlag, 1991, pages 347 et seq. They are hereby introduced as a reference and are accordingly deemed to be part of the disclosure.

If the dosage form according to the invention is in multiparticulate form, the delayed-release coating is preferably applied in such a manner that the multiparticulate forms containing the active ingredient are coated, after the production thereof, with the

particular polymers and optionally further auxiliary substances from aqueous and/or organic media, preferably from aqueous media, with the assistance of the fluidised bed method and the coating is preferably simultaneously dried at conventional temperatures in the fluidised bed.

A poly(meth)acrylate-based coating is preferably dried at temperatures in the range from 30 to 50°C, particularly preferably from 35 to 45°C. For cellulose-based coatings, such as for example ethylcellulose, drying preferably proceeds at a temperature in the range from 50 to 80°C, particularly preferably in the range from 55 to 65°C. If necessary, drying may additionally be followed by a temperature-controlled treatment in order to obtain a stable release profile.

Delayed release of the active ingredient from the dosage form according to the invention may also be achieved by embedding the active ingredient in a delayed-release matrix.

Materials which may be used for a delayed-release matrix are preferably physiologically acceptable, hydrophilic polymers, preferably cellulose ethers, cellulose esters and/or acrylic resins. Ethylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof, are particularly preferably used.

Where hydrophobic compounds are used as the delayed-release matrix, hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof may be used. Mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic compounds.

It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic matrix materials.

Component (b) as a viscosity-increasing agent may preferably also serve as a material for a delayed-release matrix, if this is permitted by the structure of the dosage form according to the invention.

Component (C) and the optionally present component (D), which serve to obtain the breaking strength of at least 500 N, preferably of at least 750 N, which is necessary according to the invention, may optionally also serve as additional delayed-release matrix materials.

Corresponding delayed-release compounds and methods for the delayed release of the dosage forms according to the invention and for the application of coatings which mask the taste and/or are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical Dosage Forms - Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

The dosage forms according to the invention are suitable for oral, vaginal or rectal, preferably oral, once daily administration to humans and animals.

The dosage form according to the invention may assume multiparticulate form, preferably the form of microtablets, micropellets, granules, spheroids, beads or pellets, optionally packaged in capsules or press-moulded into tablets. The multiparticulate forms preferably have a size or size distribution in the range from 0.1 to 3 mm, particularly preferably in the range from 0.5 to 2 mm. Depending on the desired dosage form, conventional auxiliary substances (B) are optionally also used for the formulation of the dosage form.

In a further preferred embodiment, the dosage form according to the invention assumes the form of a tablet, a capsule or is in the form of an oral osmotic therapeutic system (OROS), preferably if at least one further abuse-preventing component (a)-(f) is also present.

The abuse-proofed, solid dosage form according to the invention is preferably produced by mixing components (A), (C), optionally (D), optionally at least one of the additional abuse-preventing components (a) – (f) and optionally further auxiliary substances (B), in particular the delayed-release matrix compounds, wherein components (a)-(f), if necessary, are mixed separately with component (C) and optionally (D) and the resultant mixture(s) are formed, optionally after pelletisation, into the dosage form by application of force with preceding or simultaneous exposure to heat.

The pelletisation may be performed by a melt method or by wet pelletisation.

This mixture or these mixtures of the components of the dosage form according to the invention may be performed in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

The resultant mixture(s) are preferably directly formed into the dosage form according to the invention by application of force with preceding or simultaneous exposure to heat. The mixture may, for example, be formed into tablets by direct tabletting. In direct tabletting with simultaneous exposure to heat, the tabletting tool, i.e. bottom punch, top punch and die, are briefly heated at least until the polymer (C) softens and in the course of this pressed together. In direct tabletting with preceding exposure to heat, the material to be press-moulded is heated immediately prior to tabletting at least to the softening temperature of component (C) and then pressed.

The resultant mixture(s) of components (A), (C), optionally (D), the optionally present components (a) – (f) and optionally further auxiliary substances (B), in particular the delayed-release matrix compounds, may also first be pelletised and then formed into the dosage form according to the invention by application of force with preceding or simultaneous exposure to heat.

It is also possible to form the resultant mixture containing the active ingredient and/or one or more of the pharmaceutically acceptable salts thereof (A) and optionally

physiologically acceptable auxiliary substances (B), such as components (a) to (f) and optionally the delayed-release matrix compounds and at least one synthetic or natural polymer (C) and optionally a wax (D), into the dosage form by application of force, optionally to singulate the formed articles and optionally in each case to grade them by size and, after or during heating to at least the softening point of component (C), to expose them to force until the formed articles exhibit a breaking hardness of at least 500 N, preferably of at least 750 N, optionally to provide them with a cover, optionally with a delayed-release coating and optionally to mix all the formed articles together again. Such a procedure is also the object of the International Patent Application PCT/EP2004/014679, the corresponding disclosure of which is hereby introduced as a reference and should therefore be deemed to be part of the disclosure of the present application. It is known to the person skilled in the art that, in doing so, by use of antioxidants it is possible to forgo the maintenance of an inert gas atmosphere during the production process (?).

Moreover, the necessary heating of the mixture and/or the formed articles may be achieved with the assistance of ultrasound before or during the necessary application of force to achieve the breaking hardness or hardness according to the invention of at least 500 N, preferably of 750 N. A corresponding procedure is disclosed in the International Patent Application PCT/EP2005/004225 and is hereby introduced as a reference and is thereby deemed to be part of the disclosure of the present application.

If components (c) and/or (d) and/or (f) are present in the dosage form according to the invention, care must be taken to ensure that they are formulated in such a manner or are present in such a low dose that, when correctly administered, the dosage form is able to bring about virtually no effect which impairs the patient or the efficacy of the active ingredient.

If the dosage form according to the invention contains component (d) and/or (f), the dosage must be selected such that, when correctly orally administered, no negative effect is caused. If, however, the intended dosage of the dosage form is exceeded inadvertently, in particular by children, or in the event of abuse, nausea or an inclination to vomit or a bad flavour is produced. The particular quantity of component

(d) and/or (f) which can still be tolerated by the patient in the event of correct oral administration may be determined by the person skilled in the art by simple preliminary testing.

If, however, irrespective of the fact that the dosage form according to the invention is virtually impossible to pulverise, the dosage form containing the components (c) and/or (d) and/or (f) is provided with protection, these components should preferably be used at a dosage which is sufficiently high that, when abusively administered, they bring about an intense negative effect on the abuser. This is preferably achieved by spatial separation of at least the active ingredient used from components (c) and/or (d) and/or (f), wherein the active ingredient is preferably present in at least one subunit (X) and components (c) and/or (d) and/or (f) are present in at least one subunit (Y), and wherein, when the dosage form is correctly administered, components (c), (d) and (f) do not exert their effect on taking and/or in the body and the remaining components of the formulation, in particular component (C) and optionally (D), are identical.

If the dosage form according to the invention comprises at least 2 of components (c) and (d) or (f), these may each be present in the same or different subunits (Y). Preferably, when present, all the components (c) and (d) and (f) are present in one and the same subunit (Y).

In the case of spatial separation into subunit(s) (X) and subunit(s) (Y) and irrespective of the arrangement of these subunits in the dosage form, a subunit (X) contains the active ingredient in delayed-release form, such that said active ingredient ensures controlled release with once daily administration.

For the purposes of the present invention, subunits are solid formulations, which in each case, apart from conventional auxiliary substances known to the person skilled in the art, contain the active ingredient, at least one polymer (C), optionally a wax (D) and optionally at least one of the optionally present components (a) and/or (b) and/or (e) or in each case at least one polymer (C) and the antagonist(s) and/or emetic(s) and/or component (e) and/or component (f) and optionally at least one of the optionally present components (a) and/or (b) and optionally the delayed-release

matrix compounds. Care must here be taken to ensure that each of the subunits is formulated in accordance with the above-stated process.

One substantial advantage of the separated formulation of the active ingredient used from components (c) or (d) or (f) in subunits (X) and (Y) of the dosage form according to the invention is that, when correctly administered, components (c) and/or (d) and/or (f) are hardly released on taking and/or in the body or are released only in such small quantities that they exert no effect which impairs the patient or therapeutic success or, on passing through the patient's body, they are only liberated in locations where they cannot be sufficiently absorbed to be effective. When the dosage form is correctly administered, preferably hardly any of components (c) and/or (d) and/or (f) is released into the patient's body or they go unnoticed by the patient.

The person skilled in the art will understand that the above-stated conditions may vary as a function of the particular components (c), (d) and/or (f) used and of the formulation of the subunits or the dosage form. The optimum formulation for the particular dosage form may be determined by simple preliminary testing. What is vital is that the particular subunits contain the polymer (C) and optionally (D) and have been formulated in the stated manner.

Should, contrary to expectations, the abuser succeed in comminuting such a dosage form according to the invention, which comprises components (c) and/or (e) and/or (d) and/or (f) in subunits (Y), for the purpose of abusing the active ingredient and obtain a powder which is to be extracted with a suitable extracting agent, not only the active ingredient but also the particular component (c) and/or (e) and/or (f) and/or (d) will be obtained in a form in which it cannot readily be separated from the active ingredient, such that when the dosage form which has been tampered with is administered, in particular by oral and/or parenteral administration, it will exert its effect immediately on taking and/or in the body combined with an additional negative effect on the abuser corresponding to component (c) and/or (d) and/or (f) or, when the attempt is made to extract the active ingredient, the coloration will act as a deterrent and so prevent abuse of the dosage form.

A dosage form according to the invention, in which the active ingredient is spatially separated from components (c), (d) and/or (e), preferably by formulation in different subunits, may be formulated in many different ways, wherein the corresponding subunits may each be present in the dosage form according to the invention in any desired spatial arrangement relative to one another, provided that the above-stated conditions for the release of components (c) and/or (d), on the one hand, and for release of the active ingredient, namely controlled release for once daily administration, on the other, are fulfilled.

The person skilled in the art will understand that component(s) (a) and/or (b) which are optionally also present may preferably be formulated in the dosage form according to the invention both in the particular subunits (X) and (Y) and in the form of independent subunits (Y') corresponding to subunits (X) and (Y), provided that neither the abuse-proofing of the dosage form nor the active ingredient release over 24 hours in the event of correct administration is impaired by the nature of the formulation and the polymer (C) is included in the formulation and formulation is carried out in accordance with the above-stated processes.

In a preferred embodiment of the dosage form according to the invention, subunits (X) and (Y) are present in multiparticulate form, wherein microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets are preferred and the same form, i.e. shape, is selected for both subunit (X) and subunit (Y), such that it is not possible to separate subunits (X) from (Y) by mechanical selection. The multiparticulate forms are preferably of a size in the range from 0.1 to 3 mm, preferably of 0.5 to 2 mm.

The subunits (X) and (Y) in multiparticulate form may also preferably be packaged in a capsule or be press-moulded into a tablet, wherein the final formulation in each case proceeds in such a manner that the subunits (X) and (Y) are also retained in the resultant dosage form.

The respective multiparticulate subunits (X) or (Y) of identical shape should also not be visually distinguishable from one another so that the abuser cannot separate them from one another by simple sorting. This may, for example, be achieved by the application of identical coatings which, apart from this disguising function, may also

incorporate further functions, such as, for example, delayed release of the active ingredient or provision of a finish resistant to gastric juices or taste masking on the particular subunits.

In a further preferred embodiment of the present invention, subunits (X) and (Y) are in each case arranged in layers relative to one another.

The layered subunits (X) and (Y) are preferably arranged for this purpose vertically or horizontally relative to one another in the dosage form according to the invention, wherein in each case one or more layered subunits (X) and one or more layered subunits (Y) may also be present in the dosage form, such that, apart from the preferred layer sequences (X)-(Y) or (X)-(Y)-(X), any desired other layer sequences may be considered, optionally in combination with layers containing components (a) and/or (b).

Another preferred dosage form according to the invention is one in which subunit (Y) forms a core which is completely enclosed by the delayed-release subunit (X), wherein a separation layer (Z) may be present between said layers. Such a structure is preferably also suitable for the above-stated multiparticulate forms, wherein both subunits (X) and (Y) and an optionally present separation layer (Z), which must satisfy the hardness requirement according to the invention, are formulated in one and the same multiparticulate form.

In a further preferred embodiment of the dosage form according to the invention, the subunit (X) forms a core, which is enclosed by subunit (Y), wherein the latter comprises at least one channel which leads from the core to the surface of the dosage form.

The dosage form according to the invention may comprise, between one layer of the subunit (X) and one layer of the subunit (Y), in each case one or more, preferably one, optionally swellable separation layer (Z) which serves to separate subunit (X) spatially from (Y).

If the dosage form according to the invention comprises the layered subunits (X) and (Y) and an optionally present separation layer (Z) in an at least partially vertical or horizontal arrangement, the dosage form preferably takes the form of a tablet, a coextrudate or a laminate.

In one particularly preferred embodiment, the entirety of the free surface of subunit (Y) and optionally at least part of the free surface of subunit(s) (X) and optionally at least part of the free surface of the optionally present separation layer(s) (Z) may be coated with at least one barrier layer (Z') which prevents release of component (c) and/or (e) and/or (d) and/or (f). The barrier layer (Z') must also fulfil the hardness conditions according to the invention.

Another particularly preferred embodiment of the dosage form according to the invention comprises a vertical or horizontal arrangement of the layers of subunits (X) and (Y) and at least one push layer (p) arranged therebetween, and optionally a separation layer (Z), in which dosage form all of the free surfaces of the layer structure consisting of subunits (X) and (Y), the push layer and the optionally present separation layer (Z) are provided with a semipermeable coating (E), which is permeable to a release medium, i.e. conventionally a physiological liquid, but substantially impermeable to the active ingredient and to component (c) and/or (d) and/or (f), and wherein this coating (E) comprises at least one opening for release of the active ingredient in the area of subunit (X).

A corresponding dosage form is known to the person skilled in the art, for example under the name oral osmotic therapeutic system (OROS), as are suitable materials and methods for the production thereof, inter alia from US 4,612,008, US 4,765,989 and US 4,783,337. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

An osmotic dosage form containing an analgesic opioid and a dye as an aversive agent is likewise known to the person skilled in the art from the prior art (WO 03/015531). The tablet core preferably consists of two layers, an opioid-containing layer and a push layer, wherein the push layer contains the dye as the aversive

agent. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

In a further preferred embodiment, the subunit (X) of the dosage form according to the invention is in the form of a tablet, the edge face and optionally one of the two main faces of which is covered with a barrier layer (Z') containing component (c) and/or (d) and/or (f).

The person skilled in the art will understand that the auxiliary substances of the subunit(s) (X) or (Y) and of the optionally present separation layer(s) (Z) and/or of the barrier layer(s) (Z') used in each case in formulating the dosage form according to the invention will vary as a function of the arrangement thereof in the dosage form according to the invention, the mode of administration and as a function of the active ingredient present or of the optionally present components (a) and/or (b) and/or (e) and of component (c) and/or (d) and/or (f), while maintaining release of the active ingredient over 24 hours. The materials which have the properties necessary in each case are known per se to the person skilled in the art.

If release of component (c) and/or (d) and/or (f) from subunit (Y) of the dosage form according to the invention is prevented with the assistance of a cover, preferably a barrier layer, the subunit may consist of conventional materials known to the person skilled in the art, providing that it contains at least one polymer (C) and optionally the component (D) to fulfil the hardness condition of the dosage form according to the invention.

If a corresponding barrier layer (Z') is not provided to prevent release of component (c) and/or (d) and/or (f), the materials of the subunits should be selected such that release of the particular component (c) and/or (d) from subunit (Y) is virtually ruled out.

The materials which are stated below also to be suitable for production of the barrier layer may preferably be used for this purpose.

Preferred materials are those which are selected from the group comprising alkylcelluloses, hydroxyalkylcelluloses, glucans, scleroglucans, mannans, xanthans, copolymers of poly[bis(p-carboxyphenoxy)propane and sebacic acid, preferably in a molar ratio of 20:80 (marketed under the name Polifeprosan 20®), carboxymethylcelluloses, cellulose ethers, cellulose esters, nitrocelluloses, polymers based on (meth)acrylic acid and the esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, halogenated polyvinyls, polyglycolides, polysiloxanes and polyurethanes and the copolymers or mixtures thereof.

Particularly suitable materials may be selected from the group comprising methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose acetate, cellulose propionate (of low, medium or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethylcellulose, cellulose triacetate, sodium cellulose sulphate, polymethyl methacrylate, polyethyl methacrylate, polybutyl methacrylate, polyisobutyl methacrylate, polyhexyl methacrylate, polyisodecyl methacrylate, polylauryl methacrylate, polyphenyl methacrylate, polymethyl acrylate, polyisopropyl acrylate, polyisobutyl acrylate, polyoctatdecyl acrylate, polyethylene, low density polyethylene, high density polyethylene, polypropylene, polyethylene glycol, polyethylene oxide, polyethylene terephthalate, polyvinyl alcohol, polyvinyl isobutyl ether, polyvinyl acetate and polyvinyl chloride.

Particularly suitable copolymers may be selected from the group comprising copolymers of butyl methacrylate and isobutyl methacrylate, copolymers of methyl vinyl ether and maleic acid of high molecular weight, copolymers of methyl vinyl ether and maleic acid monoethyl ester, copolymers of methyl vinyl ether and maleic anhydride and copolymers of vinyl alcohol and vinyl acetate.

Further materials which are suitable for formulating the barrier layer are starch-filled polycaprolactone (WO98/20073), aliphatic polyesteramides (DE 19 753 534 A1, DE 19 800 698 A1, EP 0 820 698 A1), aliphatic and aromatic polyester urethanes (DE

19822979), polyhydroxyalkanoates, in particular polyhydroxybutyrates, polyhydroxyvalerates), casein (DE 4 309 528), polylactides and copolylactides (EP 0 980 894 A1). The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

The above-stated materials may optionally be blended with further conventional auxiliary substances known to the person skilled in the art, preferably selected from the group consisting of glyceryl monostearate, semi-synthetic triglyceride derivatives, semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinylpyrrolidone, gelatine, magnesium stearate, stearic acid, sodium stearate, talcum, sodium benzoate, boric acid and colloidal silica, fatty acids, substituted triglycerides, glycerides, polyoxyalkylene glycols and the derivatives thereof.

If the dosage form according to the invention comprises a separation layer (Z'), said layer, like the uncovered subunit (Y), may preferably consist of the above-stated materials described for the barrier layer. The person skilled in the art will understand that release of the active ingredient or of component (c) and/or (d) from the particular subunit may be controlled by the thickness of the separation layer.

The dosage form according to the invention exhibits controlled release of the active ingredient over at least 24 hours and is therefore suitable for once daily administration.

Method for determining breaking strength

In order to verify whether a material may be used as component (C) or (D) respectively, the material is press-moulded to form a tablet with a diameter of 10 mm and a height of 5 mm using a force of 150 N at a temperature which at least corresponds to the softening point of the polymer and is determined with the assistance of a DSC diagram of the material. Using tablets produced in this manner, breaking strength is determined with the apparatus described below in accordance with the method for determining the breaking strength of tablets published in the European Pharmacopoeia 1997, page 143, 144, method no. 2.9.8. The apparatus used for the measurement is a "Zwick Z 2.5" Zwick materials tester, materials tester Fmax = 2.5 kN with a draw of max. 1150 mm, which is to be adjusted through a setup with the assistance of a column and a spindle, a clearance behind of 100 mm, a test speed that can be adjusted to between 0.1 and 800 mm/min and a testControl software. Measurement was performed using a pressure piston with screw-in inserts and a cylinder (diameter 10 mm), a force transducer, Fmax. = 1 kN, diameter = 8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M to DIN 55350-18 (Zwick gross force Fmax = 1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany), the order no. for the tester being BTC-FR 2.5 TH. D09, the order no. for the force transducer being BTC-LC 0050N. P01, the order no. for the centering device being BO 70000 S06.

Figure 1 shows the measurement of the breaking strength of a tablet, in particular the adjusting device (6) for the tablet (4) used for this purpose before and during measurement. For this purpose, the tablet (4) is between the upper pressure plate (1) and the lower pressure plate (3) of the device (not shown) for applying force with the assistance of two fixing devices consisting of 2 parts, which are each fixed to the upper or lower pressure plate after setting the distance (5) necessary for the reception and centering of the tablet to be measured (not shown). To set the distance (5), the fixing devices consisting of 2 parts may each be moved horizontally outward or inward on the pressure plate, on which they are seated.

The tablets deemed to be resistant to breaking under a specific action of force include not only those which have not broken but also those which may have suffered plastic deformation under the action of the force.

The breaking strength of the dosage forms obtained according to the invention is determined using the same measurement method, wherein the dosage forms other than tablets are also tested.

The invention is explained below with reference to Examples. These explanations are given merely by way of example and do not restrict the general concept of the invention.

Example 1

Production of an abuse-proofed tablet containing (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol

The quantities of active ingredient hydrochloride, polyethylene oxide powder and hydroxypropylmethylcellulose (Metholose 90 SH 100 000) as the delayed-release matrix material listed in Table 1 were mixed in a free-fall mixer. The tabletting tool, which consisted of die, top punch and bottom punch with a diameter of 13 mm, was heated to 90°C in a heating cabinet. 600 mg portions of the powder mixture were press-moulded by means of the heated tool, the pressure being maintained for at least 15 seconds.

Table 1

Components	Per tablet	Complete batch
Active ingredient HCl	200.0 mg	60.0 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	360.0 mg	138.0 g
Hydroxypropylmethylcellulose 100 000 mPas (Metholose 90 SH 100 000)	40.0 mg	12.0 g
Total weight	600.0 mg	210.0 g

The breaking strength of the tablets was determined using the above-described method. No breakage occurred when a force of 500 N was applied. The tablets could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

In vitro release from the tablets produced

In vitro release of active ingredient hydrochloride from the tablets produced was determined in a paddle stirrer apparatus with sinker according to the method described in the European Pharmacopoeia. The temperature of the release medium was 37°C and the rotational speed of the stirrer 75 min^{-1}. The release medium used

was 600 ml of intestinal juice, pH 6.8. The quantity of active ingredient hydrochloride released in each case into the dissolution medium at any one time was determined by spectrophotometry. The percentage released quantity, relative to the total quantity of active ingredient hydrochloride, at each point in time is shown in Table 2.

Table 2

Time, min.	Released quantity, wt.%
30	12
240	42
480	65
720	80
1080	94
1440	99

Amended claims:

1. An abuse-proofed, oral dosage form with a breaking strength of at least 500 N and with a controlled release of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol for once daily administration, characterised in that it comprises the active ingredient and/or at least one of the pharmaceutically acceptable salts or derivatives thereof (A), at least one synthetic and/or natural polymer (C), optionally at least one delayed-release matrix material and/or optionally at least one delayed-release coating, at least one further physiologically acceptable auxiliary substance (B), optionally at least one wax (D), component (C) or (D) in each case exhibiting a breaking strength of at least 500 N.

2. A dosage form according to claim 1, characterised in that the hydrochloride, sulphate, hydrobromide, saccharinate, the salt from the methanesulphonic acid, the formic acid, the acetic acid, the oxalic acid, the succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid or aspartic acid and the active ingredient is present as the salt.

3. A dosage form according to claim 1 or 2, characterised in that hydrochloride of the active ingredient is present as the salt.

4. A dosage form according to claim 1, characterised in that the corresponding ester, ether and/or the corresponding amide is present as the derivative of the active ingredient.

5. A dosage form according to claims 1 to 4, characterised in that the corresponding stereoisomers of the active ingredient are present.

6. A dosage form according to any one of claims 1 to 5, characterised in that it is in the form of a tablet.

7. A dosage form according to any one of claims 1 to 5, characterised in that it is in multiparticulate form, preferably in the form of microtablets, micropellets, granules, spheroids, beads or pellets, optionally press-moulded into tablets or packaged in capsules.

8. A dosage form according to any one of claims 1 to 7, characterised in that the polymer (C) is at least one polymer selected from among the group comprising polyalkylene oxides, polyethylenes, polypropylenes, polyvinyl chlorides, polycarbonates, polystyrenes, poly(meth)acrylates and the copolymers thereof and mixtures of at least two representatives of the stated polymer classes or polymers.

9. A dosage form according to claim 8, characterised in that the polyalkylene oxide is a polymethylene oxide, polyethylene oxide and/or polypropylene oxide.

10. A dosage form according to any one of claims 1 to 9, characterised in that a polyethylene oxide of high molecular weight is present as the polymer (C).

11. A dosage form according to any one of claims 1 to 10, characterised in that the polymer (C) is a water-soluble or water-swellable polymer.

12. A dosage form according to any one of claims 1 to 11, characterised in that the polyethylene oxide (C) has a molecular weight of at least 0.5 million.

13. A dosage form according to claim 12, characterised in that the molecular weight of the polyethylene oxide (C) is at least 1 million.

14. A dosage form according to claim 12, characterised in that the molecular weight of the polyethylene oxide (C) is 1-15 million.

15. A dosage form according to any one of claims 1 to 13, characterised in that the polymer component (C) is used in a quantity of at least 20 wt.%, preferably in a quantity of 35 to 99.9 wt.%, particularly preferably in a quantity of at least 50 wt.%, very particularly preferably of at least 60 wt.%, relative to the total weight of the dosage form.

16. A dosage form according to any one of claims 1 to 15, characterised in that the wax (D) is at least one natural, semi-synthetic and/or synthetic wax with a softening point of at least 60°C.

17. A dosage form according to claim 16, characterised in that the wax (D) is carnauba wax or beeswax.

18. A dosage form according to any one of claims 1 to 17, characterised in that the component(s) (C) and optionally (D) are present in such quantities that the dosage form exhibits a breaking strength of at least 500 N.

19. A dosage form according to any one of claims 1 to 18, characterised in that the active ingredient is present in a delayed-release matrix.

20. A dosage form according to claim 19, characterised in that component (C) and/or component (D) also serves as the delayed-release matrix component.

21. A dosage form according to any one of claims 1 to 20, characterised in that at least one auxiliary substance (B) serves as a material for the delayed-release matrix.

22. A dosage form according to any one of claims 1 to 21, characterised in that it comprises a coating, preferably a delayed-release or taste-masking coating.

23. A dosage form according to any one of claims 1 to 22, characterised in that it comprises at least one of the following abuse-preventing components (a)-(f) as the auxiliary substance (B):

(a) at least one substance which irritates the nasal passages and/or pharynx,

(b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, preferably as an aqueous extract obtained from the dosage form, forms a gel which preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

(c) at least one antagonist for the active ingredient with potential for abuse,

(d) at least one emetic,

(e) at least one dye as an aversive agent,

(f) at least one bitter substance.

24. A dosage form according to claim 23, characterised in that the irritant according to component (a) causes burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli.

25. A dosage form according to claim 23 or 24, characterised in that the irritant according to component (a) is based on one or more constituents of at least one hot substance drug.

26. A dosage form according to claim 25, characterised in that the hot substance drug is at least one drug selected from the group consisting of Allii sativi bulbus (garlic), Asari rhizoma cum herba (Asarum root and

leaves), Calami rhizoma (calamus root), Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper), Curcumae longae rhizoma (turmeric root), Curcumae xanthorrhizae rhizoma (Javanese turmeric root), Galangae rhizoma (galangal root), Myristicae semen (nutmeg), Piperis nigri fructus (pepper), Sinapis albae semen (white mustard seed), Sinapis nigri semen (black mustard seed), Zedoariae rhizoma (zedoary root) and Zingiberis rhizoma (ginger root), particularly preferably at least one drug from the group consisting of Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper) and Piperis nigri fructus (pepper).

27. A dosage form according to claim 25 or 26, characterised in that the constituent of the hot substance drug is present as an o-methoxy(methyl)phenol compound, an acid amide compound, a mustard oil or a sulphide compound or is derived from such a compound.

28. A dosage form according to any one of claims 25 to 27, characterised in that the constituent of the hot substance drug is at least one constituent selected from the group consisting of myristicin, elemicin, isoeugenol, β-asarone, safrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, piperine, preferably trans-piperine, glucosinolates, preferably based on non-volatile mustard oils, particularly preferably based on p-hydroxybenzyl mustard oil, methylmercapto mustard oil or methylsulphonyl mustard oil, and a compound derived from these constituents.

29. A dosage form according to any one of claims 23 to 28, characterised in that the component (b) is at least one viscosity-increasing agent selected from the group comprising microcrystalline cellulose with 11 wt.% carboxymethylcellulose sodium (Avicel® RC 591), carboxymethylcellulose sodium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), locust bean flour (Cesagum® LA-200, Cesagum® LID/150,

Cesagum® LN-1), pectins from citrus fruits or apples (Cesapectin® HM Medium Rapid Set), waxy maize starch (C*Gel 04201®), sodium alginate (Frimulsion ALG (E401)®), guar flour (Frimulsion BM®, Polygum 26/1-75®), iota-carrageenan (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat 150 ®), tara stone flour (Polygum 43/1®), propylene glycol alginate (Protanal-Ester SD-LB®), apple pectin, sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide welan gum (K1A96) and xanthan gum (Xantural 180®).

30. A dosage form according to any one of claims 23 to 29, characterised in that the component (c) is at least one opiod antagonist.

31. A dosage form according to any one of claims 23 to 30, characterised in that the emetic according to component (d) is based on one or more constituents of ipecacuanha (ipecac) root, preferably on the constituent emetine, and/or is apomorphine.

32. A dosage form according to any one of claims 23 to 31, characterised in that the component (e) is at least one physiologically acceptable dye.

33. A dosage form according to any one of claims 23 to 32, characterised in that the component (f) is at least one bitter substance selected from the group comprising aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol and mixtures thereof, fruit aroma substances, preferably from lemons, oranges, limes, grapefruit and mixtures thereof, and mixtures thereof of at least 2 components, denatonium benzoate and mixtures thereof of at least 2 components.

34. A dosage form according to any one of claims 23 to 33, characterised in that the active ingredient (A) is present spatially separated from, preferably without direct contact with the component (c) and/or (d) and/or

(f), wherein the active ingredient or the active ingredients (A) are preferably present in at least one subunit (X) and components (c) and/or (d) and/or (f) are present in at least one subunit (Y), and, when the dosage form is correctly administered, components (c) and/or (d) and/or (f) from the subunit (Y) do not exert their effect in the body or on taking.

35. A process for the production of a dosage form according to any one of claims 1 to 34, characterised in that

(1) components (A), (C), optionally (B) and optionally (D) and optionally delayed-release matrix compounds are mixed, wherein the optionally present components (a) to (f), if necessary, are mixed separately with addition of component (C) and optionally (D),

(2) the resultant mixture or mixtures, optionally after pelletisation, are formed into the dosage form by application of force and with preceding or simultaneous exposure to heat and are optionally provided with a delayed-release coating.

36. A process according to claim 35, characterised in that pelletisation is performed by a melt method.

37. A process according to claim 35, characterised in that pelletisation is performed by wet pelletisation.

38. A process for the production of a dosage form according to any one of claims 1 to 34, characterised in that

(1) a mixture containing components (A), (C), optionally (B) and optionally (D) and optionally delayed-release matrix compounds and the optionally present components (a) to (f) as a separate mixture is formed into formed articles by application of force,

(2) the formed articles obtained are optionally singulated and optionally in each case graded by size and

(3) after or during heating at least until component (C) softens, the formed articles are exposed to action of force until the formed articles exhibit breaking hardness of at least 500 N,

(4) are optionally provided with a coating, optionally a delayed-release or taste-masking coating and the formed articles are optionally all mixed together again.

39. A dosage form obtainable by processes according to one or more of claims 35 to 38.

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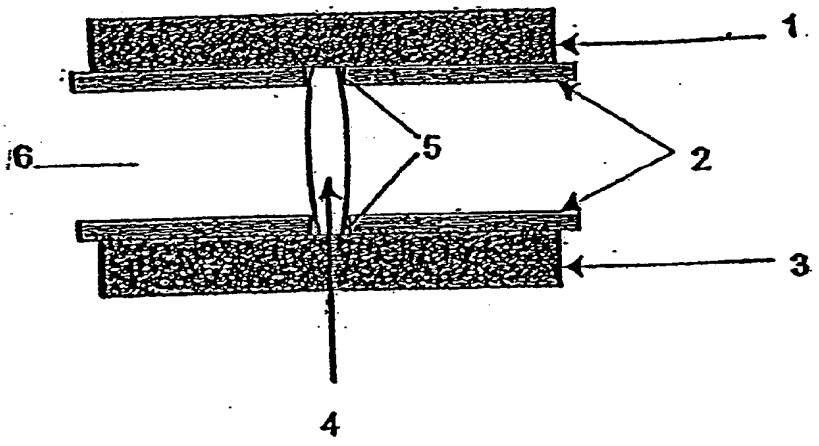

FIG..1